PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IL2005/000043	13.01.2005	15.01.2004

International Patent Classification (IPC) or both national classification and IPC
C07F9/6584, C07F9/113, A61K31/661

Applicant
BIOLAB LTD.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 30,35,43,44,54,55,56 (in part)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 30,35,43,44,54,55,56 are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☒ the claims, or said claims Nos. 30,35,43,44,54,55,56 are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 30,35,43,44,54,55,56 (in part)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	30,35
	No:	Claims	1-29,31-34,36-56
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-56
Industrial applicability (IA)	Yes:	Claims	1-56
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Present claims 30,35,43,44,54,55,56 relate to formulae (3), (4), (5), (6), and (7) in which the substituents Z, R1, R2, and R4 are defined by reference to a desirable characteristic or property, namely "protecting group" and "hydrophobic group".
The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Moreover, the initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible.

Consequently, the search has been restricted to the compounds according to formulae (3)-(7) as exemplified in the description and the use of example 5a according to claims 55 and 56.

A complete international preliminary examination of the present application is limited to those parts of the claims for which a complete international search report was established (Rule 66.1(e) PCT). It should in particular be understood that any positive statement as to novelty and/or inventive step exclusively relates to said limited subject-matter.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: LORENZ, PETER ET AL: "Synthesis of N-Lost derivatives. II. Reaction of N,N-bis(2-chloroethyl)phosphoramidic dichloride with 1-aminopropane-2,3-diol" ARCHIV DER PHARMAZIE (WEINHEIM, GERMANY) , 319(11), 1023-7 CODEN: ARPMAS; ISSN: 0365-6233, 1986, XP008045159

D2: DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SHIBAGAMI, MOTONARI ET AL: "Preparation of sphingolipids for pharmaceuticals and cosmetics" XP002323215 retrieved from STN Database accession no. 2004:17805

D3: WO 95/21848 A (THE UNITED STATES OF AMERICA, REPRESENTED BY THE) 17 August 1995 (1995-08-17)

D4: WO 93/19760 A (THE BIOMEMBRANE INSTITUTE) 14 October 1993 (1993-10-14)

D5: RAMSTEDT, BODIL ET AL: "Comparison of the biophysical properties of racemic and D-erythro-N-acyl sphingomyelins" BIOPHYSICAL JOURNAL , 77(3), 1498-1506 CODEN: BIOJAU; ISSN: 0006-3495, 1999, XP002323211

D6: HANS-PETER DEIGNER AND BEATRIX FYRNYS: "Rapid synthesis of 2-desoxy-2-amino-3-phosphocholine-glycerin ic-acid-alkylester, 1-alkyl-1-desoxy- and 1-o-alkyl-2-desoxy-2-amino-sn-glycero-3-ph osphocholines, -3-phospho-N,N'-dimethylethanolamine and -3-phospho-Fmoc-serine-methylester" CHEMISTRY AND PHYSICS OF LIPIDS, vol. 61, 1992, pages 199-208, XP002323214

D7: H.P. DEIGNER AND B. FYRNYS: "Synthesis of [32P]-labelled 1-O-alkyl-2-desoxy-2-amino-sn-glycero-3-ph osphocholines" JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMCEUTICALS, vol. 34, no. 2, 1994, pages 185-190, XP008045160

D8: C.M. THOMPSON ET AL: "Synthesis, Configuration, and Chemical Shift Correlation of Chiral 1,3,2-Oxazaphospholidin-2-ones Derived from L-Serine" JOURNAL OF ORGANIC CHEMISTRY, vol. 55, 1990, pages 111-116, XP002323263

D9: ZHENG-JIE HE ET AL: "Synthesis of novel optically active cyclic phospholipid conjugates of tegafur and uridine starting from L-serine" PHOSPHORUS, SULFUR AND SILICON, vol. 160, 2000, pages 223-232, XP008045147

V.1. Novelty:

V.1.1. Present claims 1-29, 31-34, 36-42, 45-53 relate to formulae (1) and the process for preparing sphingomyelin derivatives using the compound of formula (1), in which the substituents Z, R1, R2, R4 and X are also defined by reference to a desirable characteristic or property, namely "protecting group", "hydrophobic group", and "leaving group".

Again, the subject-matter for which protection is sought is not clearly defined (Article 6 PCT). The claims attempt to define the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.

The use of these terms prevents the invention from being clearly distinguished from the prior art with respect to novelty and/or inventive step.

In this context, it has to be furthermore noted that a product is not rendered novel merely by the fact that it is produced by means of a new process: the use of a different parameter, i.e. by reference to a new process, for defining a known product does not confer novelty on the product itself.

V.1.2. When understanding the defintions of Z, R1, R2, and X in their broadest sense, the compounds disclosed in D1, D6 (examples 10 and 11), and D7 (examples 3-6) have to be

considered as falling within the scope of formula (1). Therefore, the subject-matter of claims 1-14,21,22 is not novel (Article 33(2) PCT).

V.1.3. The process claimed in the present application using oxazaphospholane as intermediate for the preparation of phospholipid derivatives is known from D6 and D7. Therefore, the subject-matter of claims 15-20, 23-29, 31-34, 36-42, 45-53 is not novel (Article 33(2) PCT).

V.1.4. Documents D2 and D5 disclose the example (5a) of the present description as well as its pharmaceutical use. Therefore, the subject-matter of claims 43,44,55,56 is not novel (Article 33(2) PCT).

V.1.5. Documents D3 and D4 disclose present example (7a) and consequently, the subject-matter of claim 54 is not novel (Article 33(2) PCT).

V.1.6. The examples 3 and 4 have not been disclosed in the prior art and therefore the subject-matter of claims 30 and 35 is novel (Article 3(2) PCT).

V.2. Inventive Step:

Furthermore, the above-mentioned lack of clarity notwithstanding, the subject-matter of claims 1-56, in as far as novel, does not involve an inventive step in the sense of Article 33(3) PCT, and therefore the criteria of Article 33(1) PCT are not met:

The reaction of L-serine with POCl3 to yield oxazaphospholane which is then used as starting material for the preparation of various phospholipid derivatives is a method very well known from the prior art (see D6-D9). It would therefore have been obvious to the skilled person to use this method for preparing the sphingomyelin derivatives of the present application.

Thus, the subject-matter of present claims 1-56 cannot be considered as involving an inventive step in the sense of Article 33(3) PCT).

V.3. Industrial Applicability:

The present application relates to a process for preparing sphingomyelin-derivatives and the intermediates used in this process. The subject-matter of claims 1-56 is therefore considered as industrially applicable (Article 33(4) PCT).